REMARKS

Claim 100 has been amended. Claims 100, 102-107, 109-112, 114-117, and 119-128 are pending in the present application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 100, 102-104, 109-111, 114-115, and 120-124 under 35 U.S.C. § 112, First Paragraph

Claims 100, 102-104, 109-111, 114-115, and 120-124 stand rejected under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" for the reasons of record. This rejection is respectfully traversed.

The present invention relates to isolated nucleic acid sequences encoding a polypeptide having phospholipase B activity, selected from the group consisting of:

(a) a nucleic acid sequence encoding a polypeptide having an amino acid sequence which has at least 90% identity with amino acids 20 to 464 of SEQ ID NO:2;

(b) a nucleic acid sequence having at least 90% homology with nucleotides 568 to 2045 of SEQ ID NO:1; and

(c) a nucleic acid sequence which hybridizes under at least medium-high stringency conditions with (i) nucleotides 568 to 2045 of SEQ ID NO:1, (ii) the cDNA sequence contained in nucleotides 568 to 2045 of SEQ ID NO:1, or (iii) a complementary strand of (i) or (ii).

Applicants submit that the specification complies with the written description requirement.

It is well settled that "[t]he test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter ..." *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983).

As set forth in Federal Circuit decisions, a specification complies with the written description requirement if it provides "a precise definition, such as by structure, formula, chemical name, or physical properties of the claimed subject matter sufficient to distinguish it from other materials." See, e.g., *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997); *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). In fact, "[a] description of a genus of cDNAs may be achieved by means of a

recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Eli Lilly and Co.*, 43 U.S.P.Q.2d at 1569. The test is not whether one of ordinary skill in the art envisions all of the claimed subject matter, as suggested in the Office Action.

The Federal Circuit provides that the written description requirement for a genus of DNAs is met by a recitation of a representative number of DNAs, defined by nucleotide sequence, falling within the scope of the genus or by a recitation of structural features common to the members of the genus.

It is well established in the art that the definition of a genus of genes encoding polypeptides having an enzyme activity of interest is accomplished by using structural features that show the relatedness of the genes and their encoded products. For decades the scientific community has employed three structural features to define the relatedness of genes and their products. The three structural features are (1) percent identity of the amino acid sequences encoded by the genes, (2) percent homology of the nucleic acid sequences of the genes, and (3) nucleic acid hybridizations under defined stringent conditions to identify complementary strands of genes encoding the same or similar enzyme or protein function. These structural features have been used to predict the function of polypeptides encoded by novel genes, and to place them in an existing genus.

A search of the protein databases failed to reveal any prior art phospholipase B that shares significant homology with the phospholipase B of the present invention. Thus, the phospholipase B of the instant invention (SEQ ID NO: 2) is a new genus. Limiting the literal scope of protection of such a new genus or family to the nucleic acid sequence of SEQ ID NO: 1 or the amino acid sequence of SEQ ID NO: 2 provides little incentive to an Applicant to seek patent protection because biological diversity dictates that there will be natural variation in the sequences of other homologous genes existing in nature that are structurally- and functionally-related. Biological diversity in a given gene sequence can easily be found. As genes that fulfill a similar function in different species have evolved from a common ancestor, natural variation in the nucleic acid sequence will rapidly evolve following this speciation. Sequence variation within a single species is also common. Alternatively, the skilled artisan could easily circumvent the literal scope of protection by preparing a variant containing an insertion or deletion of one or more amino acid residues and/or the substitution of one or more amino acid residues by different amino acid residues.

In the claims at issue, Applicants provide a recitation of three structural features common to the claimed genus: (1) a nucleic acid sequence encoding a polypeptide having an amino acid sequence which has at least 90% identity with amino acids 20 to 464 of SEQ ID NO:2; (2) a nucleic acid sequence having at least 90% homology with nucleotides 568 to

2045 of SEQ ID NO:1; and (3) a nucleic acid sequence which hybridizes under medium-high stringency conditions with (i) nucleotides 568 to 2045 of SEQ ID NO:1, (ii) the cDNA sequence contained in nucleotides 568 to 2045 of SEQ ID NO:1, or (iii) a complementary strand of (i) or (ii).

The Office states that the specification does not adequately describe those structural, physical and chemical characteristics of the claimed nucleic acids or the enzyme they encode to distinguish them from nucleic acid sequences which are not claimed. With due respect, this statement is without merit. The structural features are described on page 3, line 25, to page 7, line 7, and page 12, line 29, to page 13, line 8, of the specification. As mentioned above, the three structural features of percent identity at the deduced amino acid sequence level, percent homology at the DNA level, and the ability of the claimed nucleic acid sequence to hybridize under specific stringency conditions have been used for decades by persons of ordinary skill in the art to determine the relatedness of proteins and their genes with respect to structure and function to ascertain whether they belong to the same genus or family. The scientific literature abounds with disclosures of these three structural features to describe the relatedness of proteins and their genes as well as to distinguish a protein and its gene from other proteins and their genes. Moreover, annotated databases of families of structurally-related proteins with a specific biological activity have been constructed based on these structural features. For example, the CAZy database describes the families of structurally-related catalytic and carbohydrate-binding modules (or functional domains) of enzymes that degrade, modify, or create glycosidic bonds. See www.afmb.cnrs-mrs.fr/CAZY/.

The Office contends that the structural features of percent identity at the deduced amino acid sequence level, percent homology at the DNA level, and the ability of the nucleic acid sequence to hybridize under specific stringency conditions are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level. With due respect, this statement is without merit. It is well established in the art that there is a definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level. Percent identity is highly predictive of protein function and without this tool it would be impossible to make meaningful annotations of genomes in sequencing projects. Proteins that share 90% amino acid identity are known to possess the same catalytic/biochemical function which has formed the basis for genome annotation and comparative genomics. In fact, 90% identity is an extremely conservative criterion for judging functional similarity. A long history of structure-function studies has demonstrated that single domain proteins that share substantial similarity (and >30% identity) over their entire length (>80 residues) without introduction of numerous gaps are almost certainly homologous

(derive from a common evolutionary ancestor) and share the same three-dimensional structure (see Martı´-Renom MA, Stuart AC, Fiser A, Sanchez R, Melo F, Sali A. Comparative protein structure modeling of genes and genomes. *Annu Rev Biophys Biomol Struct* 2000; 29:291–325). At the 90% level of amino acid identity, orthologous enzymes in related species are virtually guaranteed to share the same catalytic function and substrate specificity. Likewise, genes that share 90% homology encode proteins with the same catalytic/biochemical function. A simple search of any public database using the criteria above for a reference protein of interest will prove that there is a definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level.

In fact, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.,* complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure,* or some combination of such characteristics." Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, 66 Fed.Reg. 1099, 1106 (Jan. 5, 2001).

In the claims at issue, each of the claimed structural features (percent identity, percent homology, and hybridization) specifies a family of structurally- and functionally-related enzymes having phospholipase B activity. Since the claimed structural features provide a correlation between function and structure, the written description requirement is satisfied.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. § 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

II. The Rejection of Claims 100, 102-104, 109-111, 114-115, 117 and 119-124 under 35 U.S.C. § 112, First Paragraph

Claims 100, 102-104, 109-111, 114-115, 117 and 119-124 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a nucleic acid sequence encoding phospholipase B wherein either the nucleic acid sequence comprises nucleotides 568 to 2045 of SEQ ID NO: 1 or the polypeptide comprises amino acids 20-464 of SEQ ID NO: 2, does not reasonably provide enablement for any other embodiments lying outside this scope for the reasons of record. This rejection is respectfully traversed.

It is well settled that "[t]he first paragraph of section 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative

examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). Moreover, "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 USPQ at 369.

"The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed ..." *Ex parte Jackson*, 217 U.S.P.Q. 804 (Bd. Pat. App. 1982).

It is also well settled that an assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974). See also *U.S. v. Telectronics*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974); *Ex parte Hitzeman*, 9 U.S.P.Q.2d 1821 (BPAI 1988).

Moreover, in the absence of any evidence or apparent reason why compounds do not possess the disclosed utility, the allegation of utility in the specification must be accepted as correct. *In re Kamal*, 158 U.S.P.Q. 320 (C.C.P.A. 1968). See also *In re Stark*, 172 U.S.P.Q. 402, 406 n. 4 (C.C.P.A. 1972) (the burden is upon the Patent Office to set forth reasonable grounds in support of its contention that a claim reads on inoperable subject matter).

The reasoning provided in the Office Action is that the specification does not establish the regions of protein structure which may be modified without affecting phospholipase B activity and the general tolerance of a polypeptide having phospholipase B activity to modification and extent of such tolerance. Applicants respectfully submit that this reasoning is not sufficient to render the claims nonenabled.

The claimed nucleic acid sequences are structurally similar because they encode a polypeptide having an amino acid sequence that is at least 90% identical with the amino acids 20 to 464 of SEQ ID NO. 2, they have at least 90% homology with nucleotides 568 to 2045 of SEQ ID NO. 1, or they hybridize under at least medium-high stringency conditions with (i) nucleotides 568 to 2045 of SEQ ID NO:1, (ii) the cDNA sequence contained in nucleotides 568 to 2045 of SEQ ID NO:1, or (iii) a complementary strand of (i) or (ii). One of

ordinary skill in the art would, therefore, expect that the claimed nucleic acids encoding polypeptides have phospholipase B activity.

Furthermore, the specification contains an extensive disclosure of techniques which are well known in the art and indeed routine for persons of ordinary skill in the art for identifying other nucleotides of the present invention. Applicants describe methods for preparing and probing DNA libraries (Example 1-2); for isolating nucleic acids encoding the phospholipases (Example 3); for determining cross-hybridization of the nucleic acids encoding phospholipases using (i) nucleotides 568 to 2045 of SEQ ID NO:1, (ii) the cDNA sequence contained in nucleotides 568 to 2045 of SEQ ID NO:1, or (iii) a complementary strand of (i) or (ii) (page 5, line 1, to page 7, line 7); for comparing the percent identity of the deduced amino acid sequences of the phospholipases to amino acids 20 to 464 of SEQ ID NO: 2 using the Clustal method according to Higgins, 1989, *CABIOS* 5: 151-153 (Example 4); for determining the degree of homology between two nucleic acid sequences using the Wilbur-Lipman method according to Wilbur and Lipman, 1983, *Proceedings of the National Academy of Science USA* 80: 726-730 (page 12, line 29, to page 13, line 8); for producing the phospholipases (Example 5); and for purifying the phospholipases and characterizing the properties of the encoded phospholipases (Examples 6-9). It is well within the skill of the art to isolate and identify the claimed nucleic acid sequences using the Applicants' disclosure.

The Office alleges that "it is <u>not</u> routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims ..." This contention may have been true many years ago, however, it is certainly not the case as of the effective filing date of this application. As of October 1999, persons of ordinary skill in the art were able to routinely produce thousands of mutants of SEQ ID NO: 1 through mutagenesis and other techniques in a short period of time. See, for example, Michael Lamsa, Nils Buchberg Jensen, and Steen Krogsgaard, *Screen Automation and Robotiocs*, in *Enzyme Functionality: Design, Engineering, and Screening*, A. Svendsen, editor, Marcel Dekker, 2003. Furthermore, at page 13, line 9, to page 14, line 4, the specification discloses how one of ordinary skill in the art could identify essential amino acids in the sequence of SEQ ID NO: 2. One skilled in the art can, therefore, predict which modifications, if any, would result in a loss of the desired activity/utility.

The Office Action also states:

> The primary issue here is whether the specification provides sufficient characteristics for the claimed invention to indicate that Applicant had possession of it and guidance on how to make it at the time the application was filed. Applicant's assertion that the disclosed method also enables how to make the claimed nucleic acids is self-serving, and Applicant has provided no evidence to support the assertion. The specification certainly does not, since no such nucleic acid other than SEQ ID NO: 1 is disclosed, and it was not isolated by the methods Applicant refers to, i.e., involving hybridization to a probe from a nucleic acid encoding phospholipase B. Whether one of skill in the art would be able to determine after-the fact using computer algorithms

whether an particular sequence would be embraced by Applicant's claims is an issue under 35 USC 112, second paragraph, not first paragraph. In order to make such a determination, one would first have to possess the nucleic acid sequence. That Applicant even suggests one skilled in the art need make such a determination, demonstrates that Applicant was not in possession of the sequences in question. What Applicant is suggesting here is that one skilled in the art go out and clone phospholipase genes, sequence them, and then see if they meet the claim limitations. This is nothing more than a wish to know what the claim embraces, what nucleic acid sequences encode a phospholipase B.

Applicants submit that the above statements by the Examiner are simply incorrect. Example 2 demonstrates the use of a probe to identify clones expressing the phospholipase B. Applicants were not suggesting that one skilled in the art go out and clone phospholipase genes, sequence them, and then see if they meet the claim limitations. Applicants were indicating that the methods disclosed in the specification enable one skilled in the art to make and use the claimed sequences. The sequences disclosed in the specification provide the necessary tool for one skilled in the art to discover other members of this novel genus of phospholipase B molecules. Specifically, a search involving probing with (i) nucleotides 568 to 2045 of SEQ ID NO:1, (ii) the cDNA sequence contained in nucleotides 568 to 2045 of SEQ ID NO:1, or (iii) a complementary strand of (i) or (ii), is not a random search but a directed screen aimed at identifying a novel gene with the same function.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. § 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: June 14, 2004

Robert L. Starnes, Ph.D.
Reg. No. 41,324
Novozymes Biotech, Inc.
1445 Drew Avenue
Davis, CA 95616-4880
530-757-8100
530-757-4715 (direct)